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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 04/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,933	LEROY ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-42,44,46,47,51-58 and 60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-42,44,46,47,51-58 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20040308*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/8/04 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

In view of the amendment to claim 40, claim 42 has been rejoined. All claims are now directed to the invention and species elected with traverse in the paper filed 2/28/03.

Specification

The disclosure is objected to because of the following informalities:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. §§ 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821 through 1.825 for the following reasons:

The Sequence Listing is incomplete. The amino acid sequence disclosed on page 7, line 4, and page 25, line 2, and the amino acid sequence disclosed on page 28, line 29, and page 36,

line 9, are not listed, as required by 37 CFR 1.821(c). In addition, the specification fails to comply with 37 CFR 1.821(d) with regard to the nucleotide sequences shown in Fig. 7. These nucleotide sequences must be identified by their assigned SEQ ID NOs, either in the figure itself or in the 'Brief Description' of Fig. 7 (preferred).

Applicant must supply a substitute computer readable form (CRF) copy of the "Sequence Listing", a substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

Applicants are required to comply with all of the requirements of 37 C.F.R. §§ 1.821 through 1.825. Any response to this Office Action which fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. §§ 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

Claim Objections

Claims 51, 55 and 58 are objected to because of the following informalities:

Recitation of the Markush group in claims 51 and 58 is in improper format; --and -- should be inserted before "a tumor-specific promoter" in the last line of each claim.

Claim 58 is identified as being "previously presented". However it recites "104 to 1014 pfu" rather than "10^4 to 10^{14} pfu" which appeared in the previously presented claim. This appears to be a typographical error.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 42, 44, 57, 58, and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 42 and 60 are directed to adenoviral vectors that comprise an exogenous nucleotide sequence encoding a chimeric protein. The chimeric protein comprises part or all of an antibody directed against a tumor antigen or pathogenic organism with extracellular domains I and II of CD4 fused to the N-terminus of the antibody (or antibody part) and a "toxic substance" fused to the C-terminus of the antibody (or antibody part). The original specification supports a chimeric protein that comprises part or all of a generic antibody directed against a tumor antigen or pathogenic organism fused at its N-terminus to extracellular domains I and II of CD4, and supports part or all of a generic antibody directed against a tumor antigen or pathogenic organism fused to at its C-terminus to a toxic substance.

Applicant asserts that the amendment to claim 42 is supported throughout the specification and original claims. The original disclosure supports the fusion of various toxic substances to the C-terminus (or N-terminus) of a generic antibody, or part thereof, directed against a tumor antigen or pathogenic organism. However, the amendment to claim 42 also includes the amendment to claim 40, and the original disclosure does not provide any general

teachings of such a generic fusion protein also comprising extracellular domains I and II of CD4. The specification does not support fusion of both the extracellular domains I and II of CD4 and a generic toxic substance to a specific or generic antibody or part thereof. There is no general disclosure of such a chimeric protein as is recited in these claims. The original specification discloses a single species readable on these claims (e.g. pages 13, 18, and original claim 28) where the protein comprises in order from N- to C-terminus, extracellular domains I and II of CD4, the constant γ3 region (hinge regions-CH2 and CH3) of the heavy chain of the 2F5 antibody, and mature human angiogenin. One cannot pick and choose among characteristics of a specific example in hindsight, and then use the chosen characteristic as the basis of a generic claim. Single species rarely, if ever, provide support for a generic claim, as Applicant is attempting here, especially where such generic claims embrace virtually limitless species, as is the case here. *Purdue Pharma L.P. v. Faulding Inc.*, 56 USPQ2d 1481 (CAFC 2000); *In re Shokal,* 113 USPQ 283 (CCPA 1957).

Claims 44, 57 and 58 recite a protein of interest that comprises a heavy and light chain of an antibody, where both the heavy and light chains are fused at their N-termini to extracellular domains I and II of CD4. The original disclosure does not describe multimeric protein comprising a heavy and light chain, both being modified at their N-terminus by fusion to extracellular domains I and II of CD4. Page 5, lines 17-20 describes the expression of antibodies not antibodies fused to other protein moieties, such as the extracellular domains of CD4. page 6, lines 33-34, only describes preferred antibodies. Claim 59 was not an original claim or part of the original disclosure.

Applicant's arguments filed 3/8/04 have been fully considered but they are not persuasive. With respect to the rejection of claim 60, Applicant argues that "claiming an invention as broadly comprising features in the alternative does not preclude the features also appearing in combination where the features are clearly susceptible of being used in combination and where the combination is explicitly disclosed in that the features appear together in a preferred example," and alleges that one of skill would consider that the inventors were in possession of the broadly claimed embodiment. In response, the broadly described "toxic substance" and "immunopotentiating substance" are repeatedly, and consistently described throughout the original specification as alternatives, including original claims 20 through 22. Whether one of skill in the art would recognize that one could combine both a toxic substance and immunopotentiating substance in the same chimeric protein is not relevant to whether the original specification teaches such a generic embodiment. "It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose." Lockwood v. American Airlines Inc., 41 USPQ2d 1961, 1966 (CAFC 1997). The only support for these generic claims (42 and 60) is a single species (original claim 28) designed for a specific purpose, and there is no evidence of record that Applicant had contemplated the generic invention now being claimed.

Claim Rejections - 35 USC § 103

Claims 40, 41, 44, 46, 47, and 51-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allaway et al. (WO 94/19017) in view of Berkner (WO 90/01550).

Allaway discloses plasmid vectors and cells comprising same for the production of a chimeric antibodies comprising a CD4 extracellular domain (sCD4) including the CD4 leader peptide. Several types of expression construct are disclosed, the antibodies can be a homodimer of a sCD4 fused to the constant region of an IgG1 or IgG2 heavy chain, or a heterotetramer of a sCD4 fused to the constant region of an IgG1 or IgG2 heavy chain and to the constant region of kappa or lambda light chains or sCD4 fused to one of the light chain constant regions. See page 9, line 32 to page 10, line 31; page 17, line 10 to page 18, line 18; page 24, line 21, through page 30. Allaway does not disclose using adenoviral vectors to produce the chimeric antibodies.

However, Berkner had disclosed the construction of replication-defective adenoviral vectors (deletion of E1) for the expression of multimeric proteins, such as immunoglobulins, and eukaryotic host cells and viral particles comprising same. The vectors comprised an exogenous nucleotide sequence comprised a polycistronic transcription unit operably linked to expression sequences, promoters including the MLP promoter and SV40 early promoter, viral leader sequences such as the adenoviral tripartite leader located between the cistrons (and optionally a leader upstream of the first cistron) and polyadenylation sequences. Berkner discloses that the polycistronic vector system has the advantage over prior art multiple plasmid-based systems (such as that used by Allaway) in that only one vector need be used, rather than separate vectors for each subunit. This advantage avoids the necessity of using several different marker genes, and the limitation of choice of host cell (dictated by the marker genes), and is more efficient in producing desired transfectants since co-transfection of multiple vectors is less efficient than transfection of a single vector. Polycistronic adenoviral vectors have the advantage over plasmids in their ability to transfect all cells of a culture (or *in vivo*), i.e. a much higher

transfection efficiency. See pages 4-8; page 10, line 2 to page 11, line 15; page 13, line 1 to page 14, line 26.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have replaced the multiple plasmid vectors of Allaway separately encoding the heavy and light chain subunits with a single replication deficient adenoviral vector with the chimeric heavy and or light chains encoded by a single polycistronic construct, as taught by Berkner. One would have been motivated to do so for the advantages explicitly disclosed in Berkner, e.g. higher efficiency of transfection. One of skill in the art would also have been motivated to replace the single plasmid vector of Allaway encoding the chimeric heavy chain antibody with a replication defective adenovirus comprising a monocistronic construct encoding the antibody to take advantage of the higher transfection efficiency of adenoviral vectors.

This ground of rejection of claim 40 and its dependent claims had been withdrawn. However, upon further consideration it is reapplied for the following reasons. The claims recite that the part of the antibody is from an antibody directed against a tumor or an epitope specific for an infectious and pathogenic organism. However, this limitation does not distinguish the generic "part" of the antibody recited in the claim from that of Allaway. The claims do not place any restriction upon the "part" of the antibody present in the chimeric protein. The part could be the constant region of an antibody chain(s). The constant region is so named because it is common to all antibodies of that subset of antibody molecules, e.g. IgG2 antibodies, regardless of what epitope the variable region binds to. Allaway discloses that the CD4 extracellular domains are fused to the constant region(s) of the heavy and/or light chains, i.e. the variable region(s) is replaced with the CD4 moiety. However, it is the variable region of the recited

antibody that would distinguish it from a generic antibody, such as taught by Allaway. Consequently, with respect to embodiments of the claimed invention wherein only the constant region(s) of an antibody are included, the limitation as to the source of the antibody only limits it by the method of its making, not by what the part of the antibody is.

The term "pharmaceutical" recited in claims 54-56 refers to an intended use for the adenovirus which does not distinguish the composition form one that would be used in cell culture for example.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy J. Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe
Primary Examiner
Art Unit 1632